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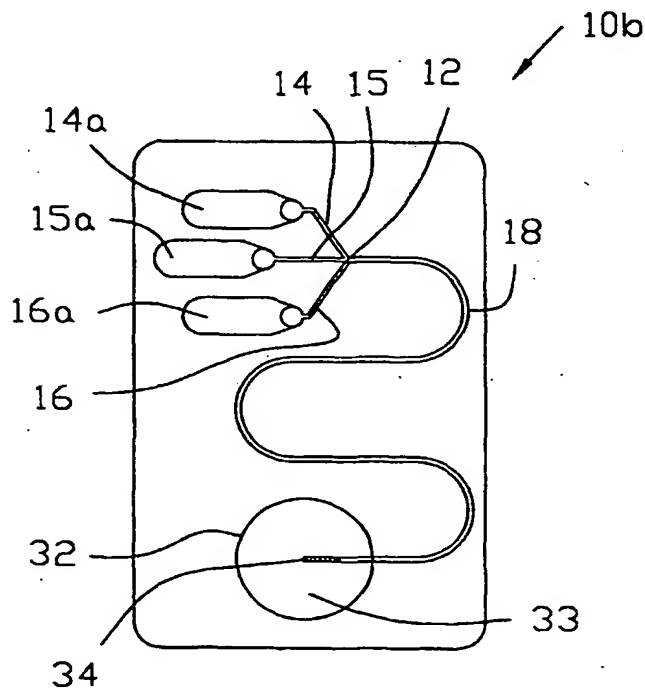
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(54) Title: PUMPLESS MICROFLUIDICS



(57) Abstract: A microfluidic device which operates without the need for an external power source. The device includes a body structure, at least one microscale channel within the structure, a port for introducing fluid into the channel, and a power source internal to the structure for propelling the fluid through the channel. Various structures are described which embody the invention.

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PUMPLESS MICROFLUIDICS

Cross-Reference to Related Applications

5 This patent application is a continuation-in-part application of U.S. Patent Application Serial No. 09/415,404, filed October 8, 1999, and also of U.S. Provisional Patent Application Serial No. 60/213,865, filed June 23, 2000 which applications are incorporated herein in their entirety by reference.

Background of the Invention

1. Field of Invention

15 This invention relates generally to microfluidic systems, and, in particular, to a microfluidic device in which the operation is conducted entirely without the benefit of an external fluidic driver.

2. Description of the Prior Art

20 Microfluidic devices have become very popular in recent years for performing analytical testing. Using tools developed by the semiconductor industry to miniaturize electronics, it has become possible to fabricate intricate fluid systems which can be inexpensively mass produced. Systems have been developed to
25 perform a variety of analytical techniques for the acquisition and processing of information.

U.S. Patent No. 5,716,852 is an example of such a device. This patent teaches a microfluidic system for detecting the presence of analyte particles in a
30 sample stream using a laminar flow channel having at least two input channels

which provide an indicator stream and a sample stream, where the laminar flow channel has a depth sufficiently small to allow laminar flow of the streams and length sufficient to allow diffusion of particles of the analyte into the indicator stream to form a detection area, and having an outlet out of the channel to form a single
5 mixed stream. This device, which is known as a T-sensor, allows the movement of different fluidic layers next to each other within a channel without mixing other than by diffusion.

Microfluidic systems of this type require some type of external fluidic driver,
10 such as piezoelectric pumps, microsyringe pumps, electroosmotic pumps and the like, to operate. It would be desirable, in many situations, to produce a device which is entirely driven by a readily available force, such as gravity, capillary action, absorption in porous materials, chemically induced pressures or vacuums (e.g., by a reaction of water with a drying agent), or by vacuum and pressure generated by
15 simple manual action, rather than by an external fluidic driver requiring a separate power source having moving parts. Such a device could be extremely simple to operate, could be manufactured very inexpensively, and could be used to perform many diagnostic assays using a variety of microfluidic methods.

20 SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a microfluidic device which can be operating without a fluid driver that requires a power source.

It is a further object of the present invention to provide a low cost disposable qualitative assay which can be adapted to medical or environmental uses, among others.

5 It is still a further object of the present invention to provide a simple microfluidic system which can perform analytical functions without the necessity of an external electrical or mechanical fluid driver system.

These and other objects are accomplished in the present invention by a
10 simple cartridge device containing microfluidic channels which perform a variety of analytical techniques for the acquisition of information without the use of any electrical or mechanical driving forces applied to the cartridge. The cartridge may be constructed from a single material, such as plastic, by conventional manufacturing methods, such as injection molding, to create a low cost device which can be
15 discarded after a single use. Inherently available forces such as gravity, hydrostatic pressure, capillary force, absorptive force manually generated pressure, or vacuum, move the fluids through the microfluidic channels to accomplish the desired analytical analyses. Other applications for this technology include toys and advertising devices.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plan view of a microfluidic device manufactured according to the present invention;

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FIG. 2 is a plan view depicting an alternative embodiment of the cartridge of FIG. 1;

FIG. 3 is another alternative embodiment of the cartridge of the present invention which is driven by absorption;

FIG. 4 is a sectional view taken along lines 4-4 of FIG. 3;

FIG. 5 is another alternative embodiment of the cartridge of the present invention which is driven by capillary action;

FIG. 6 is another alternative embodiment of the cartridge of the present invention which is driven by hydrostatic pressure;

FIG. 7 is another embodiment of the cartridge of the present invention which is driven by aspiration within the cartridge itself;

FIG. 8 is another embodiment of the cartridge of the present invention which is driven by a chemical process or a pump from within the cartridge;

FIG. 9 is another embodiment of the cartridge shown in FIG. 6 having an H-Filter within the cartridge;

FIG. 10 is a graph showing the relationship between hydrostatic pressure and Reynolds number for a typical microfluidic mixing structure;

FIG. 11 is another embodiment of the cartridge of FIG. 3 which is driven by absorption;

FIG. 12 is an enlarged view of an alternative embodiment of an absorption
5 material for use in the present invention;

FIG. 13 is another embodiment of the cartridge of the present invention exhibiting improved fluid flow within the cartridge;

10 FIG. 14 is an enlarged view of a portion of the cartridge of FIG. 13;

FIG. 15 is a graphic representation of a T-Sensor for use in the present invention;

15 FIG. 16 is a graphic representation similar to FIG. 15 showing a T-Sensor using different analytes;

FIG. 17 is a graphic representation of a T-Sensor using a readout device according to the present invention; and

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FIG. 18 is a fragmentary view of a microfluidic channel joining two reservoirs in a Y-junction constructed according to the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to FIG. 1, there is shown a cartridge generally indicated at 10 containing the elements of the present invention. Note that like parts are given like reference numerals in the embodiments contained in the present application.

Cartridge 10 is preferably constructed from a single material, such as plastic, using a method such as injection molding, and is approximately the size and thickness of a typical credit card. Located within cartridge 10 are several flow channel systems 12, preferably comprising T-Sensors which are described in detail in U.S. Patent No.

5,716,852, which disclosure incorporated by reference herein. Each T-Sensor 12 consists of a first sample channel 14, a second sample channel 16, a common channel 18, and a terminating storage chamber or reservoir 20. At the end of each channel 14, 16 opposite common channel 18 is located a circular input port 14a, 16a respectively, where droplets of reagents and samples can be placed for analysis.

In operation, T-Sensor 12 allows the movement of different fluidic layers next to each other within channel 18 without mixing other than diffusion, as fluids generally show laminar behavior within microfluidic channels. A sample solution placed in port 14a passes through channel 14 and an indicator solution placed in port 16a passes through channel 16, and the streams from channels 14, 16 merge in common channel 18 and flow next to each other until they exit into reservoir 20.

Smaller particles such as ions or small proteins diffuse rapidly across the fluid boundaries within channel 18, whereas larger molecules diffuse more slowly. Large particles, such as blood cells, show no significant diffusion within the time the two flow streams are in contact. An interface zone is formed between the fluid layers.

The signal strength of a particular optical or electrochemical property, such as fluorescence intensity of the interface zone is a function of the concentration of the analyte. In addition, it is sometimes desirable to add a third stream to T-Sensor 12, with one channel containing a reference stream for analysis purposes. This is
5 described in detail in U.S. Patent 5,948,684 , which issued September 7, 1999.

Manually operated microfluidic devices such as T-Sensor 12 can be used to qualitatively or semi-quantitatively determine analyte concentrations. A practical use may be the determination of several parameters directly in whole blood. A color
10 change in the diffusion zone of a T-Sensor detection channel can provide qualitative information about the presence of an analyte. This method can be made semi-quantitative by providing a comparator color chart with which to compare the color of the diffusion zone. This method would work somewhat similar to a paper test strip, but with much better control and reproducibility. In addition, long term
15 monitoring functions can be accomplished by placing such a device in line with a sample feed. With a T-Sensor, assays can be performed directly with whole blood, whereas paperstrip readings can be affected by the color and consistency of whole blood.

20 The accuracy of this method can be enhanced by combining the device with a readout system which may consist of an absorbance, fluorescence, chemiluminescence, light scatter, or turbidity detector placed so that the detector can observe an optically detectable change which is caused by the presence or absence of a sample analyte or particle in the detection channel. Alternatively,

electrodes can be placed within the device to observe electrochemically observable changes caused by the presence or absence of a sample analyte or particle in the in the detection channel.

5 One embodiment of this device is a disposable cartridge combined with a mass market digital camera-like detector system: a flash would illuminate the sensor area, and any type of optically detectable signal would be interpreted by image processing software and yield a chemical concentration or count output.

10 FIG. 2 shows an alternative embodiment for cartridge 10 of FIG. 1. Note that in the various embodiments, similar elements have been given similar numerals. Cartridge 10a contains four separate T-Sensor circuits 12a, 12b, 12c, 12d. These T-Sensors include common channels 16a, 16b, 16c, 16d having different configurations.

15 The driving force for operating cartridges such as those shown in FIGS. 1 and 2 is generally supplied from an external source. U.S. Patent Application Serial No. 09/080,691, which was filed on May 18, 1998, the disclosure of which is hereby incorporated by reference in its entirety, is an example of a device which requires
20 external motive forces to operate properly. Various syringe pumps located external to the cartridge are coupled to the device for operation. FIG. 3, however, shows a device which uses an internal force to drive the circuitry.

Turning now to FIG. 3, there is shown a T-Sensor 12 within cartridge 10b, substantially similar to that taught in FIG. 1. Channels 14, 16 intersect to form common channel 18 which terminates in reservoir 20. Input ports 14a, 16a are connected to channels 14, 16 respectively at the ends opposite channel 18. A
5 porous absorbent material 30 is positioned within channels 14, 16, 18 and reservoir 20 of cartridge 10b, as can be clearly seen in FIG. 4. To operate the T-Sensor of FIG. 3, a liquid sample of reagent is applied to port 14a while a liquid sample of a specimen is applied to port 16a. Material 30 acts to propel the liquids through channels 14, 16, 18 into reservoir 20. Material 30 is preferably an absorbent
10 hydrophilic substance such as cellulose, calcium chloride, calcium sulfate, or silica gel.

FIG. 11 shows another embodiment of a cartridge using the absorption principles of the present invention. Referring now to FIG. 11, cartridge 10b uses a
15 T-Sensor like device 12 having three input ports 14a, 15a, 16a coupled to channels 14, 15, 16 which converge to form common channel 18. Channel 18 terminates at a reservoir 32 which contains a circular absorbent material 33. Channel 18 is connected to reservoir 32, and thus material 33, by a series of small apertures 34, which, in the present embodiment, allow a fluid traveling within channel 18 to
20 initially reach the center of circular absorbent material 32. As fluid from channel 18 reaches material 33, material 33 acts to propel fluid through channels 14, 15, 16 and common channel into reservoir 32. In this embodiment, fluid exits from apertures 34 onto the center of material 33 and travels radially at a constant speed toward the outer circumference of circular material 33, thus providing a constant flow speed

within channel 18 as the fluid is absorbed by material 33. The absorption begins at the center of material 33, and expands exponentially the amount of absorption front as the absorption spot expands. By varying the shape, geometry, and directional preference of absorbent pad 33, the flow speed of the fluid absorbed by material 33 can be controlled as desired.

FIG. 12 shows an enlarged section of a cartridge using the absorption principles shown in FIG. 11. In this embodiment, common channel 18 terminates in a triangular section 36 of absorbent material. As fluid travels through channel 18 in the direction shown by arrow A, it reaches material 36, and since it is triangularly shaped, the length of the diffusion front is increased as diffusion progresses, thereby compensating for an increase in fluid resistance in material 36 as more fluid must pass through already wetted absorbent material. Other geometries which can be used in the present invention include hyperbolically expanding triangular shapes.

Different shapes may not only be used for both keeping the flow speed constant, but also for increasing or decreasing the flow speed, or for cyclically varying the flow speed. For example, a sinusoidal expanding "triangular" shape can be used to keep the average flow speed constant, but let it vary periodically.

The movement of fluids through cartridge 10b can be enhanced by means of a surface treatment on the walls of channels 14, 15, 16 and 18 formed by contacting the surface with low-pressure plasma. In addition, other features which enhance

fluid flow (which will be discussed in greater detail hereinafter), such as capillary forces and gravity feed, can be employed to assist this method.

Another method available for use in cartridge 10b of FIG. 11 is driven by
5 evaporation, where absorbent material 33 is not used, and reservoir 32 is exposed to the atmosphere outside cartridge 10b, where a portion of the fluid from channel 18 evaporates. If the area of fluid that is exposed to atmosphere at the outlet is larger than that at the inlet, then fluid movement will occur in principle. Alternatively, one or both of the outlet or inlet can be cooled or heated, thereby controlling the
10 evaporation rate and, thus, the fluid flow rate and direction, to maintain a constant flow rate or to vary the rate.

According to this method, the device in FIG. 11 can be operated beyond the time at which the absorptive capacity of the absorbent pad is exhausted. Reservoir 32 has a relatively large surface area, causing the evaporation of fluid at a higher rate than
15 the combined areas of inlet reservoirs 14a, 15a, and 16a. This creates a motive force, driving the fluid contained in cartridge 10b towards the apertures 34. In this embodiment, material 33 is not required for the function of this device.

The movement of fluid through a microfluidic cartridge by differential evaporation at the inlet and outlet reservoirs is, provided that all evaporation areas are kept at the
20 same temperature, only a function of the surface area of these evaporation areas. If the surfaces are liquid-filled, then the actual area differences determine the force driving the fluid movement. If the surfaces are a wetted porous material such as a filter paper, then the surface roughness also increases the effective surface area. The rougher a surface is the more "evaporative force" it creates.

The differential "evaporative force" can be enhanced by keeping the different evaporative areas at different temperatures, as evaporation is enhanced by increased temperature. For example, an inlet area at a low temperature, and an outlet area of the same size as the inlet area, but at a higher temperature, would
5 create fluid movement towards the outlet.

Alternatively, a magnetic material can be placed within reservoir 20, and the liquids applied to ports 14a, 16a comprise ferrofluids which would be propelled through channels 14, 16, 18 by magnetic forces into reservoir 20. These ferrofluids
10 could also be used in combination with reagents and specimen samples to either push or pull these fluids through T-Sensor 12 by magnetic forces.

FIG. 5 shows another alternative design for operating the T-Sensor of FIG. 1. In this embodiment, a liquid sample of reagent is applied to port 14a of cartridge
15 10c while a liquid sample of specimen is applied to port 16a. Channels 14, 16, and 18 are sized such that capillary action draws the reagent and specimen through channels 14, 16 and 18 of T-Sensor 12 into terminating reservoir 20. Channels 14, 16, and 18 preferably have dimensions between 10 nanometers and 500 micrometers in width, which act to create capillary action to power T-Sensor 12.

20 FIG. 6 is still another alternative embodiment for T-Sensor operation. In this cartridge 10d, T-Sensor 12 includes a first pressure head 40 for receiving a reagent sample and a second pressure head 42 for receiving a specimen sample. To operate T-Sensor 12, the cartridge is placed vertically and a sample of reagent is introduced

into channel 14 via head 40 and a sample of specimen introduced into channel 16 via head 42. The hydrostatic pressure present by virtue of the orientation of cartridge 10d drives the liquids through channel 18 of T-Sensor 12 and into reservoir 20. The velocity at which the liquids travel through cartridge 10d can be varied by
5 tilting the cartridge from the vertical position.

The flow of fluids within cartridge 10d of FIG. 6 can be significantly enhanced using a structural feature that uses the reservoir edges to improve the "wet-out" of the cartridge. Referring now to FIG. 13, cartridge 10d includes pressure heads 40
10 and 42 which are coupled to channels 14 and 16 respectively, which flow into common channel 18. Channel 18 eventually connects to a reservoir 20, which is preferably vented to the atmosphere external to cartridge 10d via a venting aperture 21. Connection 22 between channel 18 and reservoir 20 is a right angle bend which is located at some distance from bottom wall section 23 and reservoir 20.

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FIG. 14 is an enlarged view of the connection between channel 18 and reservoir 20. While the horizontal dimension of the channel mouth at connection 22 may be narrow or wide, vertical dimension 24 must be large enough that the surface tension of a liquid 25 flowing with channel 18 is inadequate to support a liquid drop.
20 if this requirement is fulfilled within the structure of cartridge 10d, the liquid 25 entering reservoir forms a thin stream as shown at 26 from the bottom of connection 22 and flows down the wall 27 of reservoir 20. By using this structure, pressure oscillations in channel 18 that would occur as drops form and fall within reservoir 20 is avoided, thus ensuring a smooth liquid flow.

Hydrostatically driven microfluidic circuits use gravity as their driving force. The pressure generated is a function of the difference in inlet and outlet liquid height level. This pressure is a constant for a given height difference, and generates
5 a fluid flow in the microfluidic circuit. Flow speed and flow ratios for a given pressure are largely a function of the fluid resistance in these microchannels, and of the viscosity of the solutions. For example, in a given T-Sensor, the fluid flow ratio between the two fluids will depend on the viscosity ratio of the two fluids. Blood has a viscosity about 3-4.5 times greater than that of aqueous solutions. Therefore,
10 blood will flow more slowly than an aqueous solution as the two streams flow along each other in a T-sensor channel. However, for a given hydrostatic pressure, the dividing line between the two streams will remain independent of a change of viscosity (i.e., for the same hydrostatic pressure, the dividing line will be at the center of the channel). The volumes that flow through the channel per time
15 however, are a function of their viscosity, and higher viscosity solutions will flow at a lower volume flow rate. This will eventually cause the water levels of the two inlet streams to become different, since the low-viscosity fluid will drain more quickly. This change in water levels between the two inlet streams then would have an effect on the hydrostatic pressure, and the resulting flow patterns. This can easily be
20 remedied by using comparably large volume pressure heads which change very little during the measurement time.

This phenomenon is different from flow patterns in a volume-controlled flow situation (as is usual for syringe-pump positive displacement pumps). In this case, a

constant volume flow rate will move the same amount of liquid per time through the channel. In case of different viscosities of sample and reagent, the center line will shift to the side of the lower-viscosity stream, as the higher viscosity stream flows more slowly.

5 The advantages of pressure driven flow in T-Sensors is therefore that the position of the center line is independent of viscosity. This phenomenon can be used to simplify detection in these devices.

10 One method to compensate for a change in flow speed due to a change in viscosity is to include a small "metering bubble" in the inlet channels. The time it takes to fill this bubble is proportional to the flow speed of each solution, which again is proportional to the viscosity of each solution.

15 While hydrostatic pressure is a very constant source of power for microfluidic structures, it may be necessary at times for some types of structures to overcome some initial surface effects while filling a cartridge prior to allowing gravity or capillary forces to keep the flow constant and well controlled. A variety of methods for "jump-starting" the flow can be used: tapping on the inlets, using a syringe to
20 either aspirate or press fluid into the disposable, using a "bubble pump", or a variety of other processes.

 Microfluidic cartridges can also be surface-treated (for example, by a so-called Oxygen Plasma process) to create surfaces that can be more easily wetted by
25 aqueous solutions. Such cartridges generally do not need to be "jump-started", as

the capillary forces draw fluids into these cartridges autonomously. By selective surface treatment, some areas of the cartridge can be filled, while others can create so-called surface tension valves, which require a certain amount of pressure to overcome before they wet.

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An alternate embodiment of the cartridge of FIG. 6 is shown in FIG. 7. In this cartridge 10e, a vent passage 50 is connected to reservoir 20. Vent passage 50 includes a compressible aspiration bubble pump 52 and a closure means 54. To operate T-Sensor 12 in cartridge 10e, aspiration bubble 52 is depressed while a reagent sample and a specimen sample are introduced into pressure heads 40,42. After pressure heads 40,42 are filled, closure means 54 is activated to seal vent passage 50 from atmosphere. Bubble 52 is then released causing the reagent and specimen to enter T-Sensor 12 via channels 14, 16 and 18 and into reservoir 20.

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FIG. 8 shows yet another version of the cartridge of the present invention. Cartridge 10f contains a compressible pressure bubble 60 which is connected to parts 14a and 16a via passages 62, 64 respectively, while vent passage 50 connects reservoir 20 to atmosphere. T-Sensor 12 in cartridge 10f operates as follows: bubble 60 is depressed, forcing air through passages 62, 64, and consequently causing reagent 14a and specimen in port 16a to enter T-Sensor 12 via channels 14, 16 and 18 and into reservoir 20.

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Bubble 60 can alternatively contain a liquid in equilibrium with its gas phase; some liquids, such as alcohol, acetone, methanol, have a vapor pressure high enough at room temperature to provide a constant pressure source to drive liquids

through T-Sensor 12. The pressure source will only cease once all the liquid in bubble 60 has been converted to the gas phase; until then, pressure will be constant, and only a function of temperature.

5 Another type of microfluidic device which can be readily adapted to manual operation is the H-Filter. The H-Filter structure is described in detail in U.S. Patent No. 5,932,100, the disclosure of which is hereby incorporated by reference. Manually operated H-Filters can be used to separate components from particulate-laden samples such as whole blood, or to manufacture small quantities of chemicals.

10 FIG. 9 shows a cartridge similar to FIG. 6 embodying the present invention in the form of an H-Filter. Cartridge 10g contains a first pressure head 40 for receiving a reagent sample and a second pressure head 42 for receiving a specimen sample. An H-Filter 70 is coupled to pressure heads 40, 42 via channels 14, 16 respectively.

15 H-Filter 70 consists of a channel 72 which connects channels 14, 16 to a pair of separate reservoirs 74, 76, which are connected only through a common vent 80. In the embodiment shown in FIG. 9, channel 72 of H-Filter 70 follows a serpentine path which assists in creating turbulence to enhance mixing; however, channel 72 can be straight, such as channel 16c shown in T-Sensor 12c in FIG. 2.

20 Referring now to FIG. 9, the operation of cartridge 10g will now be described. A sample, such as whole blood, is inserted into pressure head 40, while an acceptor reagent, such as water or saline is inserted into pressure head 42. Two parallel laminar streams will flow through channel 72 as the liquids ravel from channels 14,

25 16. Smaller components of the sample stream will diffuse into the acceptor stream.

The two parallel flows are then split up into separate reservoirs 74, 76 at the end of H-Filter 70. Reservoir 74 will then contain a sample solution with a reduced concentration of the extracted component, while reservoir 76 contains the acceptor reagent containing the extracted reagent at a level of some fraction of its original concentration in the sample. The contents of both reservoirs 74, 76 can then be harvested from cartridge 10g for future use, or be processed through further integrated microfluidic structures.

It may be advantageous to provide the disposables pre-filled with reagents on the cartridge. Such reagents can be placed in inlet reservoirs, and sealed with a membrane, tape, or the like. Prior to the measurement, the user fills the sample inlet reservoir, and then removes the reagent seal. This process allows the reagents to start flowing down the channel. Alternative sealing methods may be surface-tension controlled orifices which require a certain initial pressure to overcome the surface effects, and to start flowing, or other types of manual or mechanical valves.

By combining a flexible manual "bubble pump" (as shown in FIGS. 7 and 8) with a one-way valve, fluids can be pumped in a closed circuit for a period of time. This may be advantageous when extracting or washing samples or reagents, and multiple passes through a microfluidic structure would increase the yield.

Mixing solutions in manually driven microfluidic circuits can be either diffusion-based in a laminar channel (as in H-Filters and T-Sensors), or quasi-turbulent. Several structures can be used to mix solutions in a quasi-turbulent fashion. Generally, such structures consist of a succession of corners, edges, zig-zag

channels, or other features which increase the likelihood that laminar recirculation or turbulence can be generated in microchannels at the flow speeds available with a manually driven microfluidic circuit. FIG. 10 shows the relationship between hydrostatic pressure and Reynolds number for a typical microfluidic mixing structure.

5 A Reynolds number of 10 is usually sufficient to induce mixing. Turbulent or quasi-turbulent mixing is required for relatively large particles (Molecular weight of 1000 KD or more). Alternatively, bubble pumps can generate enough pressure to turbulently mix solutions in most microfluidic structures.

10 Other assay methods that lend themselves to manually driven microfluidic circuits are assays that use agglutination or sedimentation. For example, antibody-antigen complexes may either sediment into a microfluidic reservoir for detection or further processing, or they may form particles that intentionally get stuck in small microfluidic features such as orifices. The presence or absence of these complexes
15 in particular parts of the microstructures can serve as an indicator for the presence, absence, or quantity of an analyte. This could be used to develop a method for blood typing.

A simple detection method for analyzing the results of an assay performed is
20 a microfluidic format according to the present invention is shown in FIGS. 15-17. Referring now to FIG. 15, a basic T-Sensor device 12 is shown having an indicator port 14a and an analyte port 16a. Port 14a is connected to main channel 18 by a sample channel 14, while port 16a is connected to channel 18 by an analyte channel 16a. In FIG. 15, a high concentration analyte is loaded into port 16, and when T-

Sensor 12 is operated with an indicator solution within port 14, a diffusion pattern forms as shown at 90. In FIG. 16, a low concentration analyte is loaded into port 16, and a different diffusion pattern 92 is generated.

5 At some point along channel 18, the reaction between the analyte and indicator will become sufficiently intense to be seen visually. This point in channel 18, which is located some distance from channels 14a and 16a, will correlate with a particular concentration of analyte within channel 18. Optical aids, such as a magnifying lens, colored filter layer, or slit may aid on the manual visual
10 interpretation of the concentration.

 An example of a device for simple quantitation of a microfluidic device which requires no external instruments is shown in FIG. 17. Referring now to FIG. 17, a convoluted T-Sensor 12e having ports 14, 16 and channels 14a, 16a contains a main
15 channel 18a upon which a viewing window 100 has been inserted. In addition, a chart 102 is placed near T-Sensor 12e which contains indicia representative of different concentrations of the desired analyte. During operation of T-Sensor 12e, quantitation is achieved by interpreting the point at which a visible reaction has occurred at the interface between the sample and indicator. The only portion of
20 Channel 18 visible is seen through viewing window 100. In this embodiment, the analyte may be at a 4+ to 5+ amount (1+ being low, 10+ being high) because in the 6+ view area of window 100, there is barely an reaction visible.

This embodiment is aimed at providing a quantitative assessment of analyte concentration in a format that is compatible with manual performance and visual readout. This format is particularly appropriate for use with kinetic assays – in which product builds up with time – since time in a microfluidic channel corresponds to geographic distance. Examples of kinetic assays are enzyme assays, and some slow finding reactions, such as some antibody-antigen reaction. However, this technique may also work with “fast” reactions, because visual interpretation incorporates both intensity of color and “thickness” of color at the interface.

FIG. 18 shows a microfluidic device according to the present invention which joins two fluid streams in a manner which prevents the formation of air bubbles within the channels that may hamper the performance of the device. Referring now to FIG. 18, a pair of reservoirs 14a, 16a are coupled to a main microfluidic outlet channel 18 by a pair of inlet channels 14, 16 respectively. In this embodiment, channel 18 is tapered such that it is wider at section 18a where it connects to channels 14, 16. Channel 14 connects to reservoir 14a at 110, while channel 16 connects to reservoir 16a at 112.

When reservoirs 14a, 16a are initially filled, a geometry of channels 14, 16 and 18 make it difficult to avoid trapping an air bubble within channel 18, because typically the liquid in one channel flows in section 18a of channel 18 before the liquid in the other channel breaks through the surface tension barrier where the channel meets the bottom of the reservoir. As shown in FIG. 18, fluid from reservoir 14a has already reached channel 18, as shown at 114, whereas the fluid in reservoir 16a is

still trapped by the surface tension of the liquid-gas interface where reservoir 16a meets channel 16, as shown at 112.

To avoid trapping an air bubble in this microfluidic device, two constraints
5 must be addressed in the design of the microfluidic circuitry. First, the outlet channel 18 must be large enough to contain the volume of inlet channel 14 from reservoir 14a without trapping the air in channel 16. Second, the pressure differential between the pressure in outlet channel 18 and the pressure at 110, which is due to the fluid resistance to flow within channel 14, must be greater than
10 the pressure differential between the pressure in outlet channel 18 and the pressure at 112, which is due to the surface tension of the gas-liquid interface at 112. This is accomplished by narrowing the width of channel 16 as needed for the surface tension characteristic of the liquid and gas pair.

15 Surface tension valves are based on the difference in resistance contained in unwetted orifice as compared to a wetted orifice. These valves are considered "single use" valves, as once they are wetted, they behave essentially like a low resistance flow channel (dynamic resistance); however, these valves present enough resistance (static resistance) to block the fluid flow, even if some force is applied to
20 them such as pressure, capillary forces, or hydrostatic pressure. Once this static force is overcome by a "breaking force," fluid will flow through the valve.

Resistance of the inlet channels 14, 16, however, is only dynamic resistance. The more the inlet channels are filled, the higher the resistance (provided that there are no capillary forces to drive fluids through these inlet channels).

5 In operation, as the cartridge is being filled, only the resistance of one of the inlet channels 14, 16 becomes higher than the static resistance of the surface tension valve of the other inlet channel, the surface tension valve will break, and fluids from both reservoirs 14a, 16a will flow into outlet channel 18. Surface tension valves typically consist of an orifice, a channel terminating in sharp edges, or other
10 structures which create a high surface tension. Alternatively, the surface of a channel can be coated with a specific material in the valve area, thereby increasing the surface tension resistance at that point. However, the actual resistance exhibited by these valves depends to a large extent on the exact dimensions and surface properties; thus, manufacturing tolerances can have a significant impact on
15 the accuracy of these valves.

One method of improving the reliability of surface tension valves would be to provide multiple redundant surface tension valves in parallel rather than a single valve. Although the multiple valves will vary statistically in resistance, but the
20 average of the group will be close to that of a single valve. For example, by placing multiple small orifices between two channels, the same approximate surface tension can be achieved each time. FIG. 11 shows the use of multiple orifices within a channel to exhibit this principle.

Finally, an alternative design for a surface tension valve would provide a maximum breaking resistance, along with a minimum breaking resistance, for the valve.

5 The principles of the present invention can be applied to many other types of products. For example, a cartridge containing a microfluidic device as described can be used as science kits, such as a miniature chemical laboratory, for educational purposes. Another use could be as a novelty device that uses fluid flow to visualize specific patterns, such as company logos, names, signatures, and the like on a small
10 plastic card roughly the size of a standard credit card.

While the invention has been shown and described in terms of several preferred embodiments, it will be understood that this invention is not limited to these particular embodiments and that many changes and modifications may be
15 made without departing from the true spirit and scope of the invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A microfluidic device, comprising:

5 a body structure;

at least one microscale channel disposed within said structure;

means for introducing a fluid stream into said channel;

10 and driving means, internal to said structure, for propelling said fluid through said channel;

whereby said driving means requires no power source external to said
15 structure to propel said fluid.

2. The device of claim 1, wherein said driving means comprises
absorption means located within said channel such that said absorption means
propels said fluid from said introducing means through said channel.

20 3. The device of claim 2, wherein said absorption means is selected from a group consisting of cellulose, calcium chloride, calcium sulfate, and silica gel.

4. The device of claim 1, wherein said driving means comprises
25 depressible bubble pump means located within said channel.

5. The device of claim 4, wherein said bubble pump means is located within said channel such that said fluid is propelled through said channel when said bubble pump means is depressed.

5 6. The device of claim 4, wherein said bubble pump means is located within said channel such that said fluid is propelled through said channel when said bubble pump means is released after it has been depressed.

7. The device of claim 1, wherein said driving means comprises a
10 reservoir located within said channel containing a liquid which creates a vapor pressure upon converting to its gas phase for propelling said fluid.

8. The device of claim 7, wherein said liquid is selected from a group consisting of alcohol, methanol, and acetone.

15 9. The device of claim 1, wherein said fluid comprises a ferrofluid and said driving means comprises a magnetic material located within said channel.

10. The device of claim 1, wherein said body structure is fabricated from
20 plastic.

11. The device of claim 1, wherein said channel is so sized to generate capillary forces for propelling said fluid through said channel.

12. The device of claim 11, wherein the width of said channel is between 10 nanometers and 500 micrometers.

13. A microfluidic device, comprising:

5

a body structure;

a flow channel disposed within said structure having a first end and a second end;

10

a first storage means for receiving a first fluid;

a second storage means for receiving a second fluid;

15

a first inlet channel, coupling said first storage means to said flow channel at said first end;

a second inlet channel, coupling said second storage means to said flow channel at said first end;

20

a terminating reservoir coupled to said second end of said flow channel;

and driving means, internal to said structure, for propelling said first and second fluids into said terminating reservoir,

25

whereby said driving means requires no power source external to said structure to propel said first and second fluids.

14. The device of claim 13, wherein said driving means comprises an absorbent material located within said first channel, second channel, flow channel and reservoir.

5 15. The device of claim 14, wherein said absorbent material is selected from a group consisting of cellulose, calcium chloride, calcium sulfate, and silica gel.

16. The device of claim 13, wherein said driving means comprises:

10 depressible bubble pump means;

a first passageway coupling said bubble pump means to said first storage means;

15 and a second passageway coupling said bubble to said second storage means;

whereby when said bubble pump means is depressed, said first and second fluids are propelled into said terminating reservoir.

20 17. The device of claim 13, wherein said driving means comprises:

depressible bubble pump means coupled to said reservoir by a first passageway;

25 closable vent means, coupled to said bubble pump means by a second passageway, for selectively coupling said reservoir to atmosphere;

whereby when said bubble pump means is first depressed when said vent means is open, coupling said reservoir to atmosphere, said vent means is then closed, and thereafter said bubble pump means is released, said first and second fluids are propelled into said reservoir.

5

18. The device of claim 1, wherein said driving means comprises hydrostatic pressure generated by the difference in relative height of fluid levels between positions in the fluid stream along said channel.

10 19. A method of propelling a fluid through a microscale channel disposed within a structure without use of a power source external to said structure, comprising the steps of:

introducing a fluid into the microscale channel;

15

and propelling said fluid through said channel by use of driving means located within said structure.

20 20. A device for moving fluids through a microfluidic channel, comprising:

20

a microfluidic channel having an inlet and an outlet;

a fluid contained within said channel;

25 and an absorbent material to said outlet of said channel,

whereby when said fluid within said channel initially contacts said absorbent material, a driving force is created which moved said fluid through said channel to said outlet.

5

21. The device of claim 20, wherein said fluid creates a moving fluid front across said absorbent material as said fluid contacts said material.

22. The device of claim 21, wherein said absorbent material is shaped such
10 that the flow speed of said moving fluid front across said material is controlled by the shape of said material.

23. The device of claim 22, wherein said absorbent material comprises a
triangular shape and is positioned such that said moving fluid front expands as fluid
15 is absorbed, hereby increasing the driving force as fluid moved through said channel.

24. A device for providing a constant flow within a microfluidic channel,
comprising:

20 a fluid reservoir;

a first microfluidic channel connected to said reservoir;

and a first passageway for coupling said reservoir to said first channel,

whereby said first passageway is sized such that fluid entering said reservoir from said first channel flows in a smooth constant stream.

5 25. A device for providing a continuous flow within a microfluidic channel, comprising:

a fluid reservoir having a top surface and a bottom surface;

10 a first microfluidic channel connected to said reservoir;

and a first passageway for coupling said first channel to said reservoir at a position between said top surface and said bottom surface,

15 wherein said first passageway is sized such that fluid entering said reservoir from said first channel flows in a smooth, continuous stream.

26. A device for providing a visual indication of the concentration of an analyte in a microfluidic channel, comprising:

20 a microfluidic detection channel having an inlet and an outlet;

an indicator channel coupled to said detection channel at said inlet;

an indicator channel coupled to said detection channel at said inlet apposite
said indicator channel;

5 a first fluid introduced through said indicator channel into said detection
channel toward said outlet;

indicating means representative of second fluid concentration located in
proximity to said detection channel,

10 wherein when said first and second fluids flow within said detection channel
toward said outlet, a diffusion pattern is formed indicative of the concentration of
said second fluid within said detection channel such that the diffusion pattern may
be compared to said indicating means to determine concentration within said
detection channel.

15

27. The device of claim 26, wherein said indicating means further includes
a template having a plurality of viewing windows such that said diffusion pattern
within said indicator channel visible within said windows may be compared to said
indicating means to determine concentration within said channel.

20

28. A microfluidic device for joining two or more fluid streams, comprising:

a first channel having an inlet opening and an outlet opening;

a second channel having an inlet opening and an outlet opening;

and a main microfluidic channel having an inlet coupling region for
coupling said outlet openings of said first and second channels to said main channel,

5

wherein said coupling region is sized such that fluid entering said
region from either of said first or second channel outlet openings enters said main
microfluidic channel without blocking said outlet opening of said other channel.

10 29. The device of claim 28 wherein said first and second channels are sized
such that a substantial portion of the fluid contained within said channels can enter
said coupling region without blocking said outlet opening of said other channel.

15 30. The device of claim 29 wherein said outlet openings of said first and
second channels are separated by at least one diameter of one said outlet openings.

20 31. The device of claim 28 wherein said inlet opening of said first channel
is connected to a first reservoir and said inlet opening of said second channel is
connected to a second reservoir.

32. The device of claim 31, wherein said inlet openings of said first and
second channels comprise surface tension valves.

33. The device of claim 32, wherein the static resistance of said surface tension valves is lower than the dynamic resistance within said first and second channels.

5 34. The device of claim 31, further comprising driving means, internal to said first and second reservoirs, for driving fluid through said first and second channels into said main microfluidic channel.

35. A device for providing static resistance to flow in a microfluidic system,
10 comprising:

an inlet channel;

an outlet channel;

15 and a plurality of orifices, each having essentially the same dimensions, located in parallel between said inlet and outlet channels,

whereby said orifices provide a high static resistance than a single orifice but
20 a substantially lower dynamic resistance to flow.

36. The device of claim 1, wherein said driving means comprises capillary force in at least a portion of said channel.

37. The device of claim 1, wherein said driving means comprises a differential evaporation pump.

38. The device of claim 1, wherein said driving means comprises capillary
5 force in at least a portion of said channel.

1/6

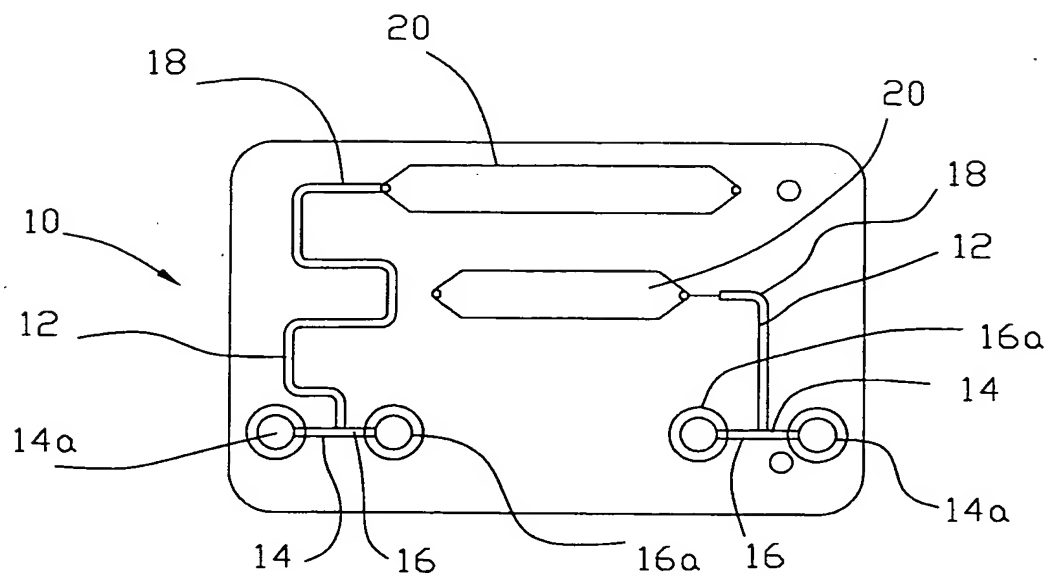


FIG. 1

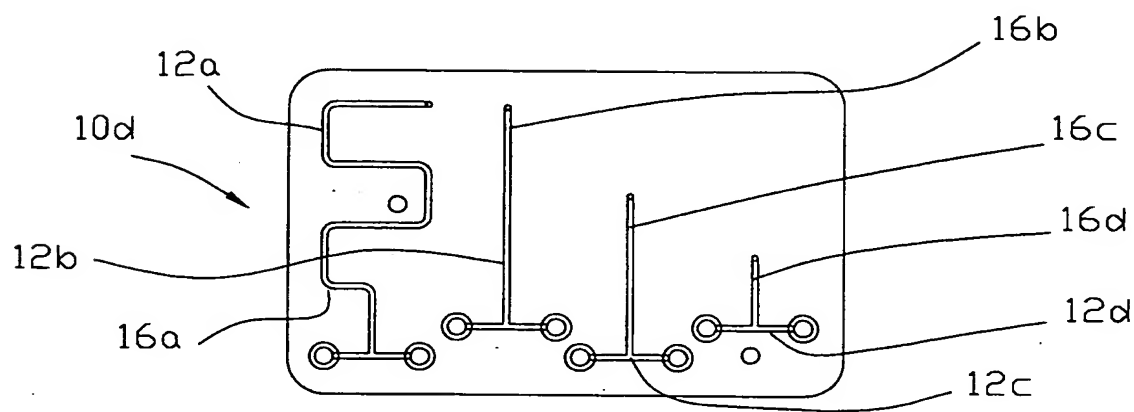


FIG. 2

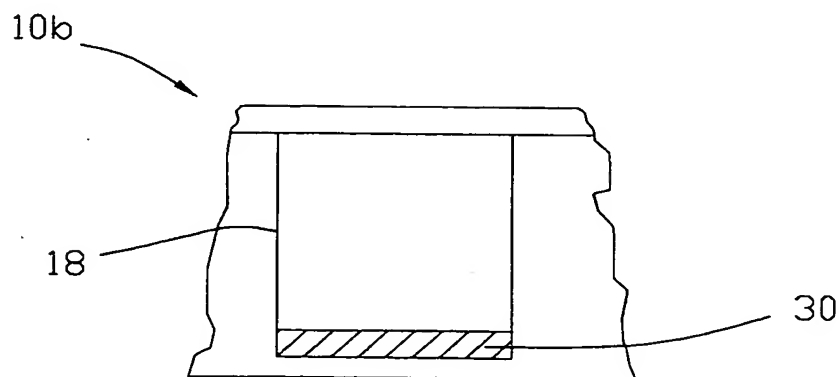


FIG. 4

SUBSTITUTE SHEET (RULE 26)

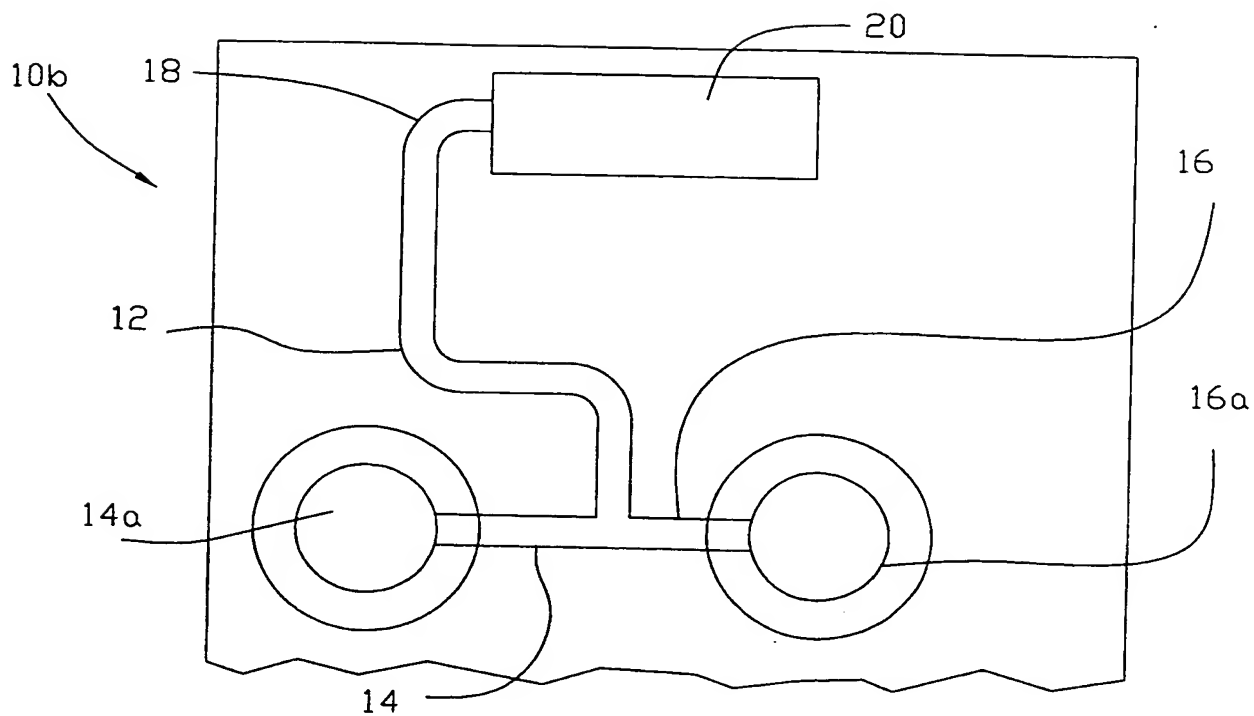


FIG. 3

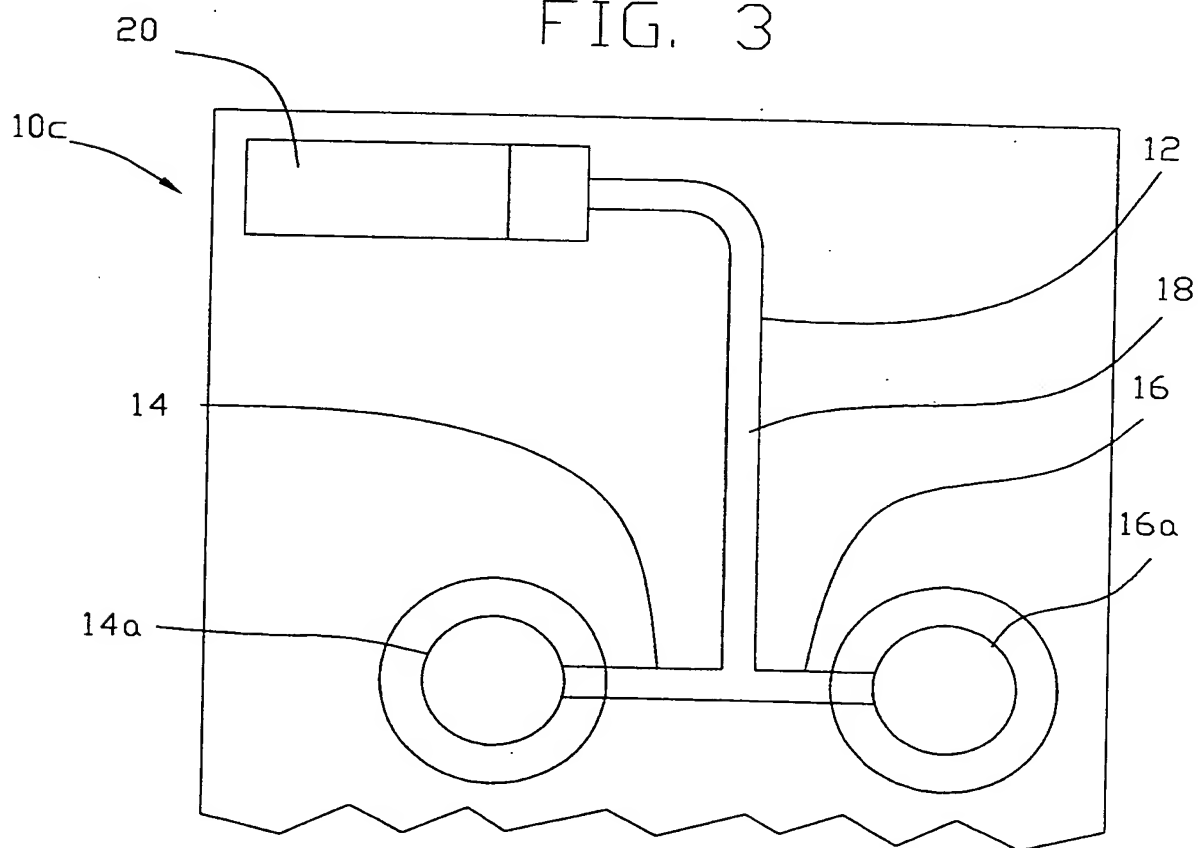


FIG. 5

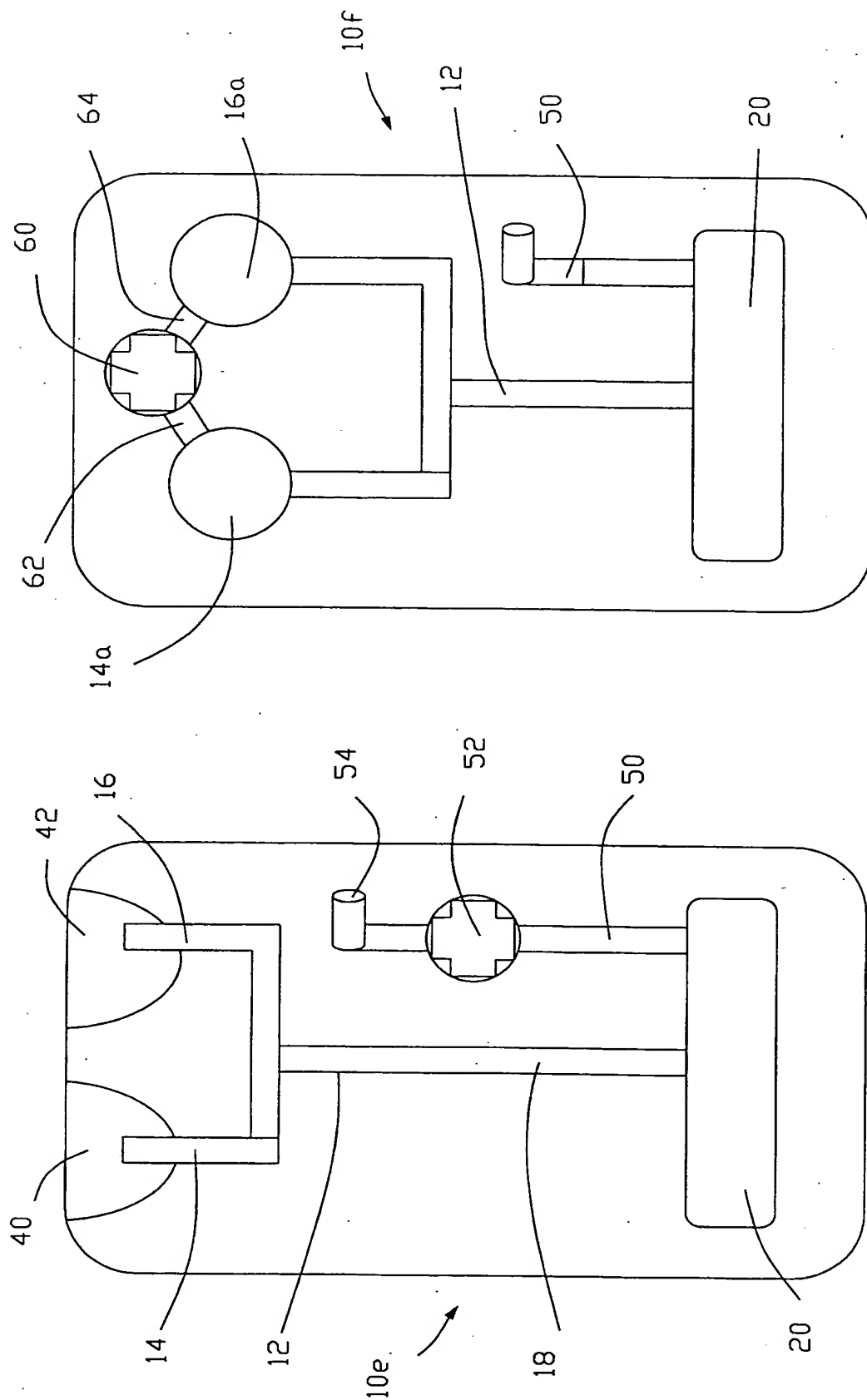


FIG. 8

FIG. 7

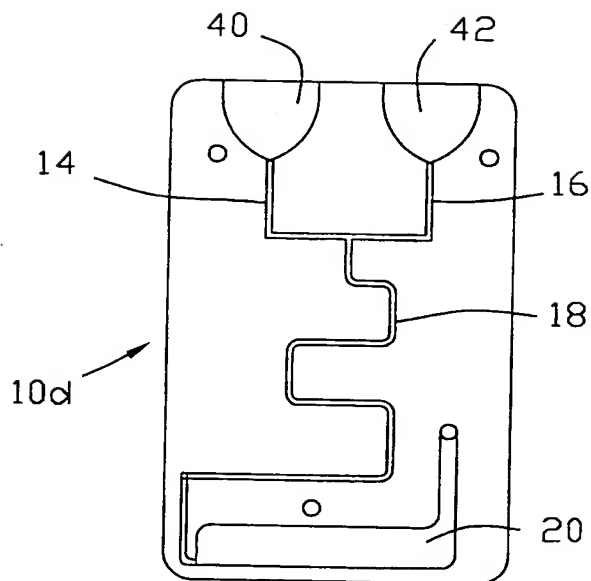


FIG. 6

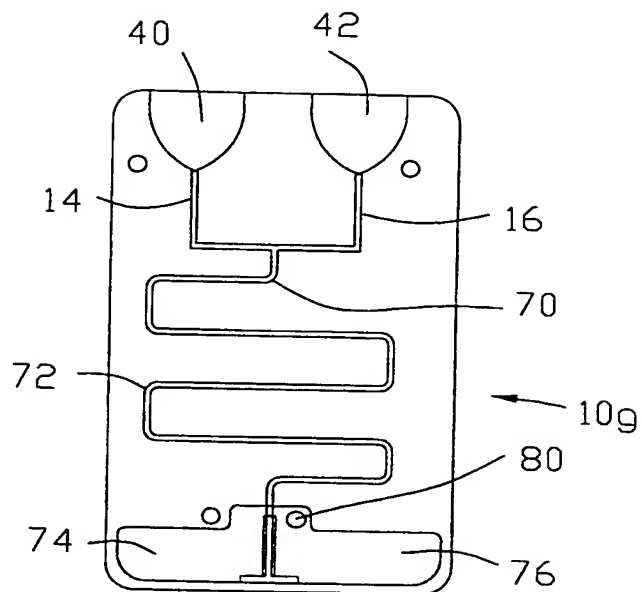


FIG. 9

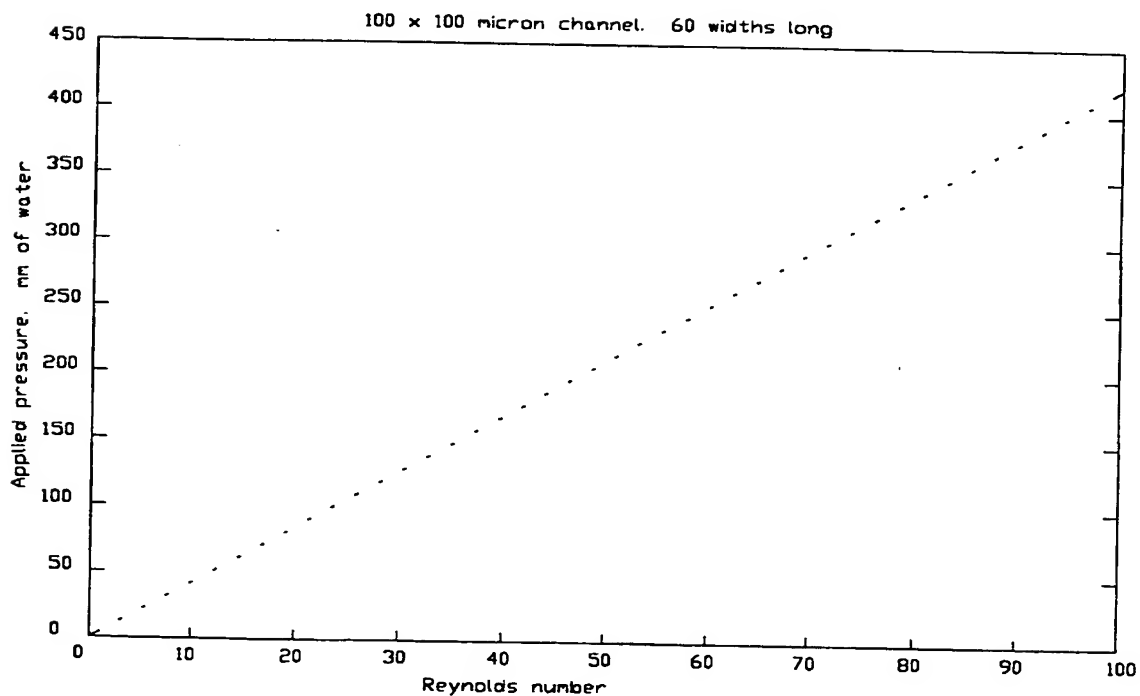
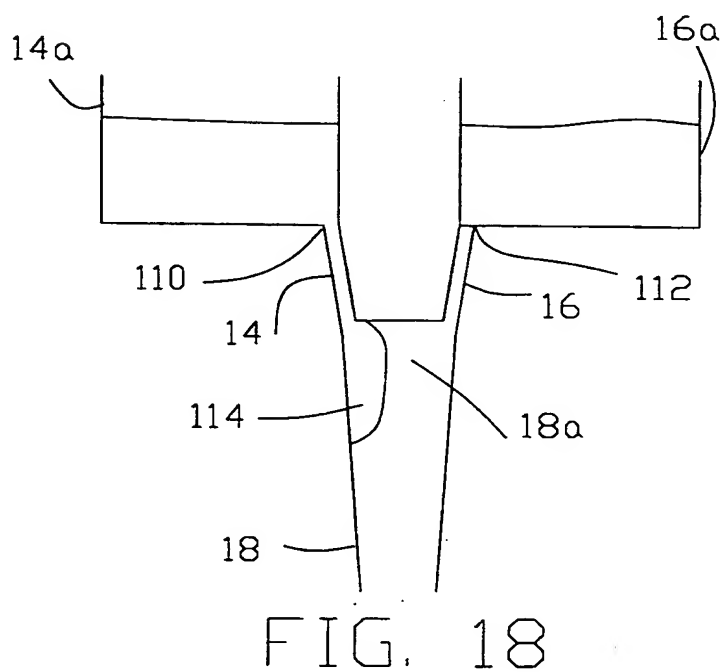
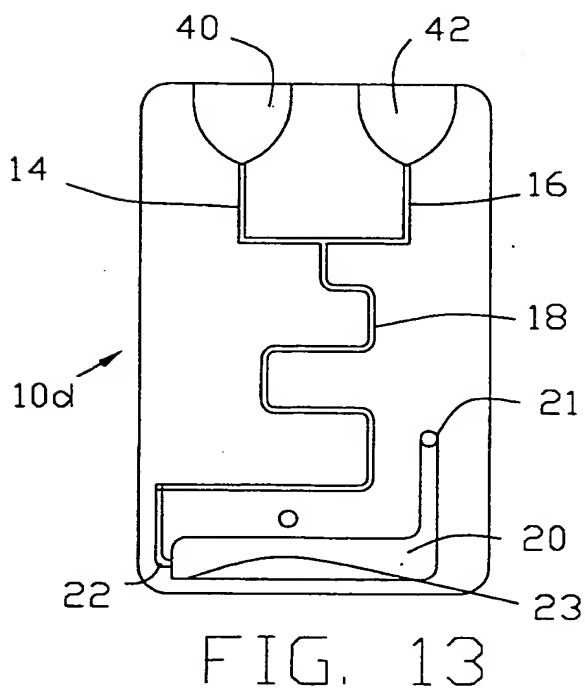
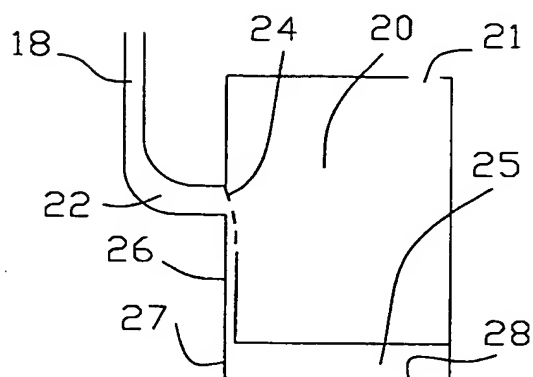
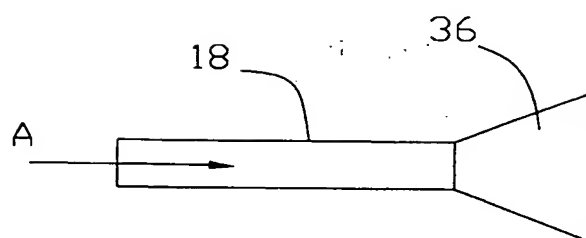
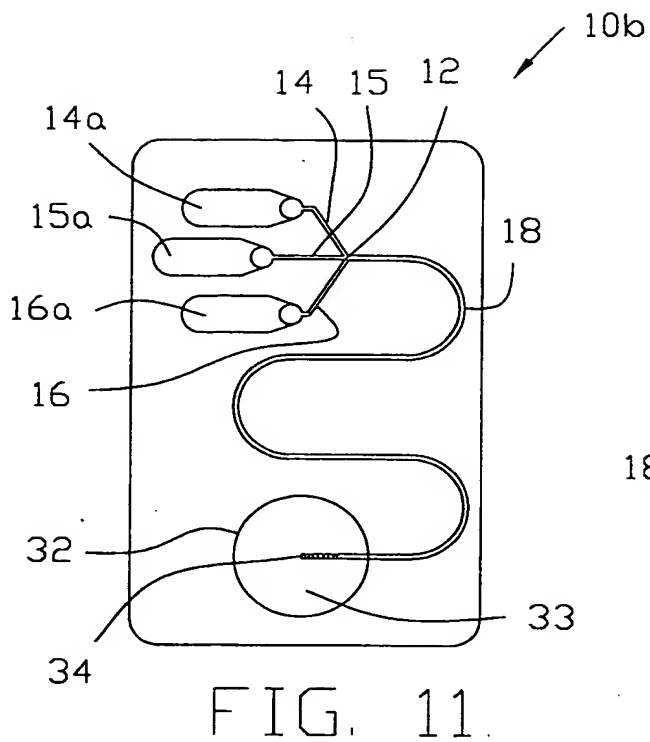
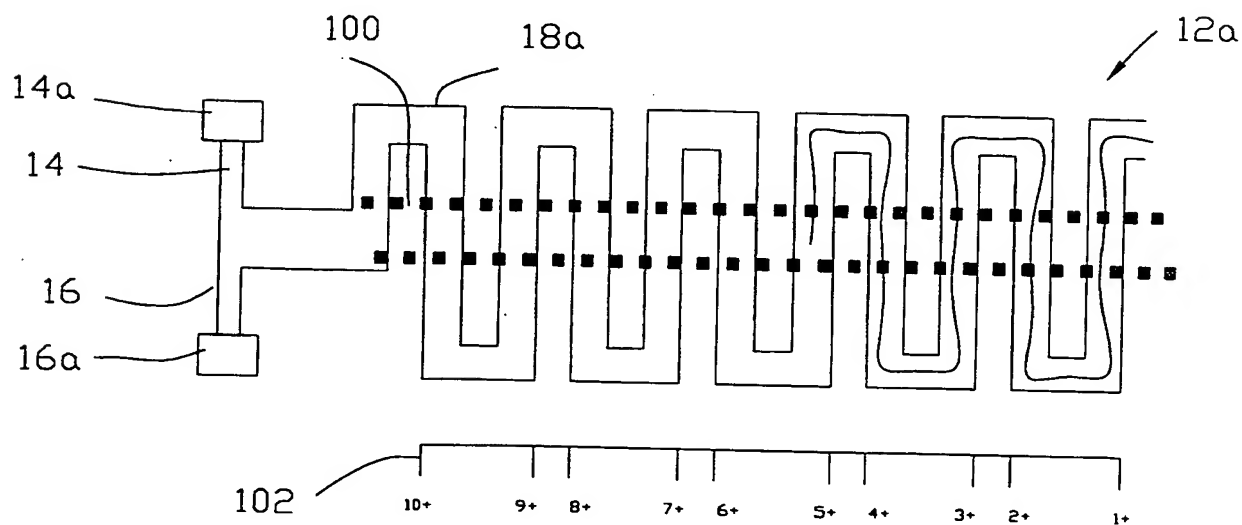
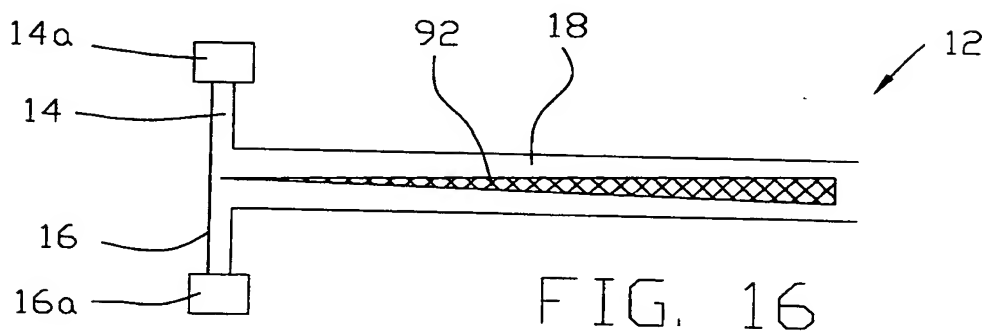
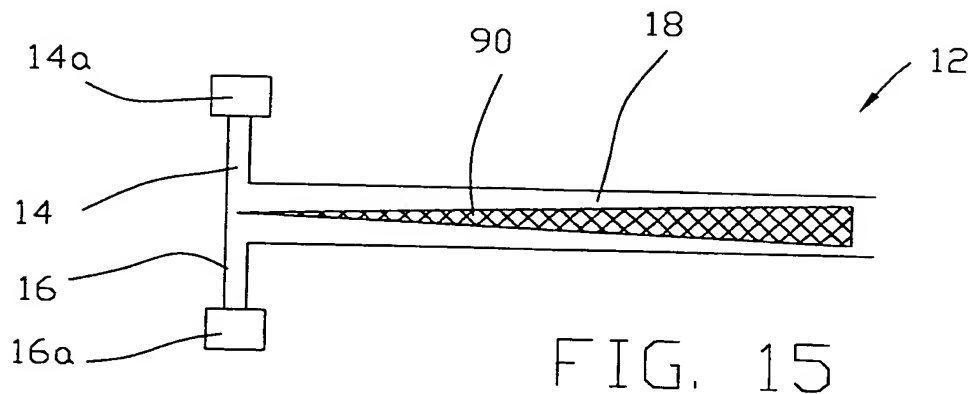


FIG. 10





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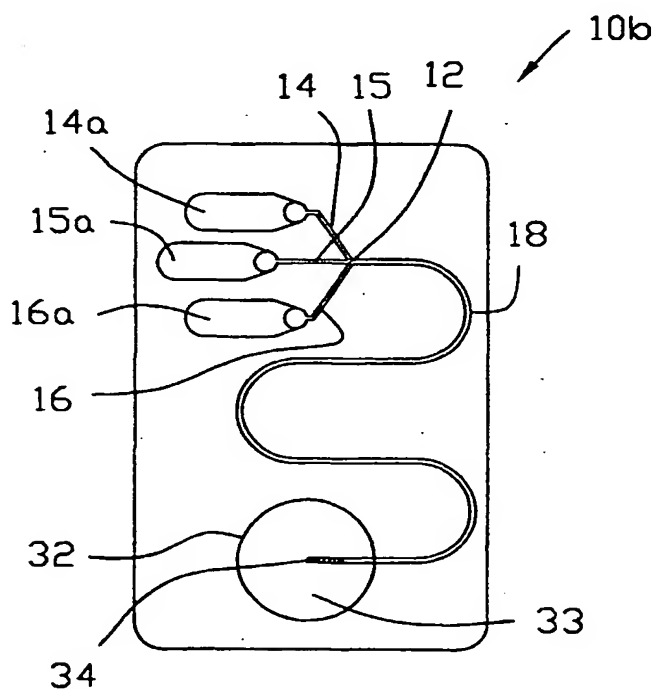
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(88) Date of publication of the international search report:
22 November 2001

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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: MICROFLUIDICS WITHOUT ELECTRICALLY OF MECHANICALLY OPERATED PUMPS



(57) Abstract: A microfluidic device which operates without the need for an external power source. The device includes a body structure, at least one microscale channel within the structure, a port for introducing fluid into the channel, and a power source internal to the structure for propelling the fluid through the channel. Various structures are described which embody the invention.

WO 01/26813 A3

INTERNATIONAL SEARCH REPORT

International Application No

PL., US 00/27898

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/00

//B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 B01L B01J B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	page 2, line 33 -page 4, line 3 page 4, line 21 -page 4, line 40 page 5, line 32 -page 9, line 35 page 10, line 7 -page 10, line 16 page 10, line 29 -page 12, line 23 page 13, line 11 -page 15, line 39 figures 1-7 --- -/--	7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

24 January 2001

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

PL, US 00/27898

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 93 17328 A (DREW SCIENT LTD) 2 September 1993 (1993-09-02)</p> <p>page 2, line 1 -page 3, line 13 page 6, line 3 -page 6, line 6 page 6, paragraph 5 -page 7, paragraph 3 page 7, paragraph 4 -page 8, paragraph 2 page 10, paragraph 2 -page 11, line 3 page 12 -page 13, paragraph 2 page 14, paragraph 3 -page 15 figures 1-4</p>	<p>1,4,5, 11,13, 19,20, 24,25, 36,38</p>
X	<p>US 5,204 525 A (HILLMAN ROBERT S ET AL) 20 April 1993 (1993-04-20)</p> <p>column 2, line 45 -column 3, line 18 column 3, line 46 -column 4, line 22 column 5, line 21 -column 6, line 49 column 6, line 57 -column 7, line 17 column 7, line 35 -column 7, line 60 column 8, line 47 -column 9, line 19 column 14, line 46 -column 15, line 3 column 18, line 58 -column 19, line 17 column 19, line 40 -column 20, line 2 column 20, line 52 -column 21, line 28 column 22, line 16 -column 22, line 63 column 28, line 20 -column 28, line 22 figures 1-5</p>	<p>1,10-13, 19,24, 25,36,38</p>
A	<p>EP 0 430 248 A (MOCHIDA PHARM CO LTD) 5 June 1991 (1991-06-05)</p> <p>page 3, line 34 -page 3, line 38 page 5, line 22 -page 6, line 23 page 7, line 38 -page 8, line 44 page 10, line 55 -page 11, line 13 page 13, line 40 -page 14, line 4 page 16, line 29 -page 16, line 36 page 17, line 20 -page 18, line 5 page 19, line 33 -page 19, line 58 figures 1-21</p>	<p>2,9</p>
X	<p>EP 0 430 248 A (MOCHIDA PHARM CO LTD) 5 June 1991 (1991-06-05)</p> <p>page 3, line 34 -page 3, line 38 page 5, line 22 -page 6, line 23 page 7, line 38 -page 8, line 44 page 10, line 55 -page 11, line 13 page 13, line 40 -page 14, line 4 page 16, line 29 -page 16, line 36 page 17, line 20 -page 18, line 5 page 19, line 33 -page 19, line 58 figures 1-21</p>	<p>1-3,10, 11, 18-20, 24,25, 36,38</p>

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INTERNATIONAL SEARCH REPORT

International Application No

PL., US 00/27898

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 0 381 501 A (EASTMAN KODAK CO) 8 August 1990 (1990-08-08)</p> <p>column 2, line 31 -column 2, line 52 column 7, line 23 -column 7, line 39 column 11, line 45 -column 12, line 18 column 12, line 53 -column 13, line 21 column 13, line 46 -column 15, line 47 column 18, line 46 -column 19, line 27 column 20, line 22 -column 21, line 18 column 21, line 36 -column 23, line 21 column 25, line 27 -column 25, line 51 figures 1,9,14,17,18 -----</p>	<p>4,9,10, 13,16, 17,20</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/27898

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-25, 36-38

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-25, 36-38

Microfluidic device for propelling fluid through channel(s) without external power source, the device containing an absorbent material at the outlet of the channel(s), the channel connected to a reservoir via a passageway which is sized for providing constant or continuous flow, and a method for propelling a fluid through a microscale channel of a structure without use of an external power source.

2. Claims: 26, 27

A device for providing visual inspection of the concentration of an analyte in a microfluidic detection channel with an inlet and outlet, comprising an indicator channel coupled to said microfluidic detection channel at its inlet which is apposite said indicator channel.

3. Claims: 28-35

Microfluidic device with first and second channels and a main channel having a coupling region sized such that fluid entering the coupling region from first or second channel outlets enters the main channel without blocking the outlet aperture of one of the two other channels, and a device for providing static flow resistance in a microfluidic system.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PL /US 00/27898

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/00/27898

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